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Treatment of Anthrax in Man: Historical and Current Concepts

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Précis

A critical evaluation of the currently recommended treatments of cutaneous, inhalation, and gastrointestinal anthrax is presented with an historical perspective. The importance of early diagnosis and specific, vigorous therapy, started on suspicion alone, is emphasized. Although Bacillus anthracis is sensitive to sulfonamides and many broad-spectrum antibiotics, the drug of choice is currently penicillin. For the treatment of septicemic anthrax, this study recommends the use of specific anti-anthrax serum to neutralize circulating toxin, as an adjunct to bactericidal antibiotics. It is also recommended that in cases of known anthrax exposure, penicillin prophylaxis should be coupled with vaccination to prevent latent infection.

Treatment of Anthrax in Man

Introduction. Anthrax is a zoonotic disease caused by the Gram-positive, nonmotile, spore-forming rod, Bacillus anthracis. Although it is primarily a disease of herbivorous animals, especially cattle, sheep, horses, goats, and wild herbivores, practically all animals are susceptible to some degree. Omnivores, such as man and swine, and carnivores, such as dogs, possess greater natural resistance to anthrax infections than herbivores. In an infected animal, virulent strains of B. anthracis produce a capsule composed of a high molecular weight polypeptide of poly-D-glutamic acid (1, 2), which acts as an aggressin by inhibiting phagocytosis (3). Virulent strains also produce a protein exotoxin composed of protective antigen, edema factor, and lethal factor (4).

Cutaneous anthrax is generally acquired through a minor scratch or abrasion of the skin by direct contact with infected animals or animal products. It can also be transmitted by biting flies which have fed on the carcasses of animals that have died of anthrax (5). Most cases of inhalation anthrax result from the inhalation of spores of B. anthracis during the processing of goat hair and wool. Gastrointestinal anthrax is caused by the consumption of inadequately cooked contaminated meat. Treatments of the three primary forms of the disease (cutaneous, inhalation, and gastrointestinal) and secondary complications (septicemia and meningitis) will be discussed in turn.

It is estimated that there are between 20,000 and 100,000 cases of human anthrax occurring annually throughout the world (6, 7). Only a fraction of human cases of cutaneous anthrax receive medical attention, so the true incidence of anthrax in man is difficult to establish. More than 6,000 cases of anthrax in humans occurred in Zimbabwe between October 1979 and March 1980

(8, 9). The distribution was reported to be: 90% cutaneous, 5% pulmonary, 5% gastrointestinal, with less than 1% meningitis. In April 1979, as many as 1,000 people died of inhalation anthrax in Sverdlovsk, USSR (10, 11).

The incidence of anthrax in man has been reduced through vaccination of livestock in endemic areas, using viable spores of the avirulent, noncapsulated Sterne strain (12) of B. anthracis, and through improved methods of disinfecting goat hair and wool imported from the Middle and Far East (13). Wright and others developed a chemical vaccine (14, 15), consisting primarily of aluminum hydroxide-adsorbed protective antigen, for workers who are occupationally exposed to anthrax. In the USSR, in addition to the chemical vaccine, a live anthrax spore vaccine (STI) has been widely used for prophylaxis against anthrax in both people and animals (16). The STI strain, developed by N. N. Ginsburg and A. L. Tamarin at the Sanitary-Technical Institute in 1940, is a capsule-free variant of B. anthracis, similar to the Sterne veterinary vaccine strain (17). As many as 2 million people per year in the USSR have been immunized against anthrax. Immunization with protective antigen followed by a booster of live vaccine produces an enhanced immunogenic effect in experimental animals (18).

Cutaneous Anthrax. The cutaneous form of anthrax, which accounts for 90 to 95% of all reported cases of anthrax in humans, takes the form of a localized, painless, central black eschar with surrounding edema. To describe this lesion, the Greek word for coal, "anthrax", was used; the French word for anthrax is "charbon" which also means coal. The most common sites for the eschar are exposed areas of the head, neck, hands and forearm. Although the black eschar is often referred to as a "malignant pustule", it is neither malignant nor pustular. Unlike a boil, pus is never present, unless there is a rare secondary infection of the lesion by pyogenic organisms.

Cutaneous anthrax is generally a self-limiting process, and the lesions heal spontaneously in 80 - 90% of the cases. However, untreated cutaneous anthrax can be associated with malignant edema and can progress to septicemia, shock, and renal failure, resulting in death in 10 - 20% of the cases. Early diagnosis and treatment with penicillin allow for an essentially 100% cure rate.

Before the advent of antibiotics, treatment of cutaneous anthrax was primarily directed at the destruction or removal of the external lesions by chemicals, cauterization and excision. Injection of anti-anthrax serum around the lesion was determined to be ineffective and was discontinued by 1932 (19). Local application of ointments containing antimicrobics has no effect. Excision and surgical tampering with cutaneous lesions are not currently recommended because they may lead to an intensification of the symptoms and possibly to the spread of infection to the surrounding tissues. The use of streptokinase to digest the eschar, and the local application of tincture of iodine or phenol is also contraindicated. The cutaneous lesions should be kept clean and covered; soiled dressings should be placed in a polyethylene bag until autoclaved or incinerated.

Dubourg and Ouary (20) claimed to have cured a patient with cutaneous anthrax by bacteriophage therapy. They did not state the source of the phage which was injected around the lesion. The possible value of bacteriophage as a therapeutic agent for anthrax was more thoroughly investigated in animal studies and found to be ineffective, even when mixed with the cells before injection (21).

Of historical interest, radiological treatment has been described by Riebeling (22) in fifteen cases of cutaneous anthrax with malignant edema. Three of these patients had previously been treated with penicillin with no

improvement. Small doses of moderately penetrating x-rays were given daily, usually to several fields. In all cases described, there was rapid improvement in both the local and general condition. However, there was no long-term follow-up to check for complications incident to treatment.

There are early reports of the successful use of arsenic preparations in the treatment of anthrax. This arseno-therapy included the use of mapharsen (oxophenarsine hydrochloride) and neosalversan (23), but the most satisfactory and widely used arsenical was neoarsphenamine (19, 24).

A number of sulfa-drugs have been used for the treatment of anthrax, including azosulfamide (Neoprontosil), sulfadiazine, sulfanilamide, sulfamerazine, sulfapyridine, and sulfathiazole (23). Sulfathiazole was the most widely recommended sulfonamide used for treating anthrax septicemia and was listed as the treatment of choice by Gold in 1942 (25). Hematuria, urticaria, and dermatitis were encountered as common adverse reactions to sulfathiazole therapy (26).

One year after the discovery of penicillin, Fleming demonstrated its effectiveness against anthrax. In 1944, Murphy, La Boccetta, and Lockwood reported the first successful use of penicillin in treating anthrax in humans (27). Various infecting strains of B. anthracis differ in their susceptibility to penicillin. In mild, uncomplicated cases, potassium penicillin V administered orally (7.5 mg/kg body weight every 6 hr for five to seven days) is sufficient (28). In most patients under penicillin treatment, the cutaneous anthrax lesion will be sterilized within 6 to 24 hr. However, in one instance, the organism was isolated 60 hr after treatment had commenced and after the patient had received a total of 3,300,000 units of penicillin (29). With more extensive disease, intramuscular procaine penicillin G (10 mg [17,000 units]/kg body weight every 12 hr for five to seven days) is recommended (30, 31). In severe cases associated with malignant edema of the

thoracic wall and neck, resulting in difficulty with respiration, intravenous hydrocortisone (100 - 200 mg/day) is recommended in addition to penicillin (32). In cases with respiratory obstruction from pressure of the edematous tissue on the trachea or larynx, tracheostomy is required.

In treating penicillin-sensitive patients or patients infected with a penicillin-resistant strain of B. anthracis, cures have been reported with sulfonamides and many broad spectrum antibiotics. Excellent results in the treatment of cutaneous anthrax have been reported with chlortetracycline, erythromycin, tetracycline, oxytetracycline, and streptomycin (33, 34). The dosages vary depending on the extent of edema and toxicity. Chloramphenicol has also been used in the treatment of cutaneous anthrax, but in some cases this therapy is not successful (9). Polymyxin and neomycin are not effective (35). Oral tetracycline (3.75 mg/kg body weight every 6 hr for five to seven days) is currently recommended for patients who cannot take penicillin (28, 36).

Inhalation Anthrax. Inhalation anthrax (Woolsorter's disease), which accounts for about 5% of all human anthrax cases, is difficult to diagnose and virtually always fatal, even with vigorous antibacterial therapy (37, 38). Fulminating cases have an onset of chills and high fever, rapidly developing vascular collapse, and pulmonary edema, leading to death within 24 to 48 hr. In some cases, the fulminant phase is preceded by 1 to 2 days with nonspecific flu-like symptoms (30, 39). If inhalation anthrax is suspected, chest x-rays should be examined for a symmetrical widening of the upper two thirds of the mediastinum as an indication of mediastinitis (40).

Treatment should be started on suspicion alone. Recovery of bacilli from the blood stream of patients with septicemia usually comes too late for therapeutic purposes (41).

Intravenous penicillin G given by continuous drip (50 mg [80,000 units]/kg body weight in the first hour, followed by 200 mg [320,000 units]/kg body weight/24 hr) has been used successfully in cases of inhalation anthrax when therapy was begun early (28). Streptomycin, 1 to 2 gm/day, given intramuscularly, may have a synergistic effect when combined with penicillin (42). Erythromycin, 1 to 4 gm/24 hr via continuous drip, is an alternate therapeutic regimen. However, even with appropriate dosage of antibiotics which sterilize the blood, the prognosis is extremely poor (37). Studies with guinea pigs have demonstrated that once the bacteremia reaches a critical value of 3×10^6 cfu/ml of blood, or 1/300th of the terminal concentration, eradication of the B. anthracis infection will not prevent a fatal outcome due to toxemia (43, 44). This is probably also true for human patients with septicemic anthrax. In well-established septicemic anthrax, it is possible that penicillin could cause the sudden release of toxin which would accelerate death.

Fortunately, the aerosol infective dose is relatively high for man. Air sampling in animal-hair mills has shown that nonimmunized workers inhaled between 150 and 700 anthrax-contaminated particles, with a diameter of 5 microns or less, during an 8-hr shift, yet clinical anthrax was very rare in these mills (45, 46). Carr and Rew (47) recovered B. anthracis from the nose and pharynx of 14 of 101 healthy workers in two goat-hair mills.

Henderson et al. (48) examined the usefulness of penicillin as a prophylactic and found that penicillin treatment did prevent the onset of pulmonary anthrax in monkeys after aerosol challenge. However, the majority of the inhaled spores remained inactive on lung epithelium and when the penicillin treatment was terminated, the animals developed anthrax and died. Combined penicillin and vaccine prophylaxis was effective. Penicillin

prophylaxis gave the host sufficient time to allow effective immunity to develop by vaccination commencing after exposure to infection.

Intestinal Anthrax. Intestinal anthrax is very rare in man and has never been documented in the United States (49). Most cases of intestinal anthrax result from eating insufficiently cooked meat from anthrax-infected animals (50). In less-developed countries it is common practice to keep animals within the walls of the yards to prevent theft or to protect the flocks from predators. Animals which show the first signs of disease are commercially utilized. After ingestion of contaminated meat, the bacilli are inactivated in the acid gastric juice, but the spores remain viable and germinate in the small intestine. An oral-oropharyngeal form of human anthrax resulting from the ingestion of raw or undercooked meat of infected animals has also been described (51).

Symptoms of gastrointestinal anthrax include nausea, vomiting, fever, abdominal pain, and in some cases bloody diarrhea. Clinically, it can mimic a bleeding peptic ulcer, peritonitis, acute gastroenteritis, or mechanical obstruction (52). In some patients, diarrhea may predominate and fluid loss through the bowel may reach the proportions of cholera with resulting hemoconcentration, massive plasma loss and renal failure (53). Gastrointestinal anthrax is associated with a 25 - 50% fatality. However, when intestinal anthrax causes eschar formation with surrounding edema of the intestinal wall, it is almost always fatal (54).

Successful management of intestinal anthrax depends on early diagnosis and efficient, vigorous therapy. However, clinical diagnosis is extremely difficult unless it is known that infected meat has been eaten (55).

In addition to fluid replacement and other supportive therapy, patients with gastrointestinal anthrax should be given penicillin by intravenous

injection according to the regimen described for treating inhalation anthrax. Tetracycline has been reported to be effective in treating some cases; the recommended dose is 1 gm intravenously every 24 hr. Intestinal perforation or intestinal obstruction can develop during late stages of the disease, requiring surgery. Prophylactic antibiotic therapy is recommended if it is known that contaminated meat has been ingested, or if B. anthracis has been inadvertently injected beneath the skin. In these cases, intramuscular administration of aqueous penicillin G (17,000 units/kg) should be given every 12 hr for five to seven days and the patient placed under surveillance for 10 days (28).

Meningeal Anthrax. Meningitis is a very rare complication of cutaneous, inhalation, or gastrointestinal anthrax. With anthrax meningitis, the regimen described for treating inhalation anthrax should be used in addition to supportive measures. However, even immediate treatment with high-dose penicillin is generally ineffective.

Haight (56) reviewed 70 cases of anthrax meningitis reported in the literature, and Levy et al. (57) have described five recent cases of anthrax meningitis in Zimbabwe. Levy et al. (57) reported that immediate treatment of patients showing clinical evidence of meningeal involvement with intravenous penicillin, 5 million units every 6 hr, chloramphenicol 500 mgs every 6 hr and sulfadiazine 1 gm every 6 hr, was ineffective.

Characteristic features include hemorrhagic meningitis with intracranial arteritis and rapid progression from onset of infection to death. The average duration of illness is two to four days (57). The terminal phase is accompanied by a state of secondary shock which becomes irreversible about 8 hr before death. Once features of meningitis are evident, death usually follows within hours.

Shanahan et al. (58) reported a case of anthrax meningitis which was successfully treated with 500 ml of anti-anthrax serum, 28 gm sulfadiazine, 110,000 units of penicillin intraspinally, and 4,400,000 units of penicillin intramuscularly.

Anti-anthrax Serum Therapy. Prior to the development of sulfonamides and antibiotics, anthrax was treated by a combination of antiserum and arsenicals (59, 60). In 1903 Scalvo first reported on the successful treatment of anthrax with serum therapy. The use of passive immunization was a considerable therapeutic advance in the treatment of anthrax and remained the most effective treatment for anthrax until the advent of sulfonamide chemotherapy nearly forty years later. The use of serum treatment lowered the mortality from anthrax in Italy from 24% to 6% (61) and from 48% to 4% in Great Britain (23, 62).

Dosages of 250 to over 1000 ml of anti-anthrax serum were recommended (63, 64). Applications were generally intramuscular, while advanced cases requiring rapid efficacy were treated intravenously. The anthrax hyperimmune serum was obtained from horses, cattle, sheep, donkeys, and mules. Although effective, prolonged morbidity from severe anaphylactic reactions was a recurrent problem. Bovine serum offered the advantage of causing serum sickness less frequently than equine serum.

Since the advent of antibiotics, medical treatment of anthrax has focused on the destruction of the bacillus and on symptomatic support. The use of anthrax antitoxin has been ignored, and anthrax antiserum is no longer commercially available in the United States. Lincoln et al. (65) noted that anthrax antiserum, available to veterinarians in England, Wales, and Scotland for treating animals, may also be used for human injection in the absence of more refined material.

Recent advances in our understanding of the cellular effects of anthrax toxin (66 - 67) and the finding that anthrax toxin is plasmid-mediated (G. B. Knudson, B. Ivins, and P. Mikesell, Abstr. Annu. Meet. Am. Soc. Microbiol. 1982, H29, p. 118) (68) have reemphasized the fact that anthrax is a toxigenic disease. In well-established septicemic anthrax, it is possible that penicillin could cause the sudden release of toxin (53). The use of specific anti-anthrax serum, which could neutralize circulating toxin that has not become irreversibly fixed, as an adjunct to antibiotic therapy, is a rational approach to the treatment of generalized anthrax infections. Lincoln and Fish (4) have suggested that antisera specific for edema factor and lethal factor combined with a protective antigen toxoid, which is immunologically active but nonlethal when combined with lethal factor would be useful in the treatment of anthrax.

Complicating Factors in the Treatment and Prevention of Anthrax. In a recent review of plasmid-determined drug resistance (69) it was concluded that it is most likely that bacteria will evolve resistance to most, if not all, antibiotics with which they are challenged. The rapidity with which bacteria adapt to antimicrobial drugs is impressive. Seroprophylaxis and serotherapy will be important in cases where B. anthracis is resistant to the normally applied antibiotics.

Immune depression from ionizing radiation increases the susceptibility of a host to anthrax infection (70). Irradiation can also result in an earlier septicemia by the release of phagocytized bacilli which were retained by the reticuloendothelial system (71).

Malnutrition, particularly lysine deficiency, is a predisposing factor for anthrax infection (72). A population with a staple diet of bread and rice would be more susceptible to anthrax than a population that includes animal protein in their diet (53).

The addition of surface-active agents, lung irritants, or immunosuppressive chemicals to anthrax spore aerosols decreases the number of spores required to cause infection. Detergents used in the industrial scouring of goat hair have been shown to enhance the respiratory virulence of B. anthracis spores by as much as 10-fold (45, 73). The addition of egg yolk enhances the virulence of B. anthracis spores injected intraperitoneally in a variety of host animals; the spores germinate and form capsules more rapidly (74, 75). There is a decreased time to septicemia and death if hydrocortisone is administered with the spores (65).

Little and Knudson recently reported that the alum-precipitated protective antigen vaccine, which is currently used to protect workers who are occupationally exposed to anthrax, protects guinea pigs from a challenge with the spores of the Vollum strain of B. anthracis, but is much less effective in protecting animals challenged with an equivalent number of spores from certain other strains of B. anthracis (S. F. Little and G. B. Knudson, Abstr. Annu. Meet. Am. Soc. Microbiol. 1984, B171, p. 46). Immunity to anthrax is not an all-or-none type of resistance but rather a graded response. The Vollum strain of B. anthracis can overwhelm immunized animals if a sufficiently large spore challenge is used. If these results can be extrapolated to man, then we can expect that the chemical vaccine will not protect people against all strains of B. anthracis or against very high aerosol concentrations.

Summary and Future Directions. Cutaneous anthrax, which is the most common form of the disease in man, is also the easiest form to recognize and to treat. Localized cutaneous anthrax responds readily to penicillin alone or in combination with streptomycin. Tetracycline can be used with patients who cannot take penicillin. Penicillin is also the drug of choice for inhalation and gastrointestinal anthrax. These forms of the disease are more difficult to diagnose and have high fatality rates. Antibiotic treatment alone is generally not successful once massive septicemia has developed. Even appropriate antibiotic therapy which sterilizes the blood will generally not prevent a fatal outcome due to toxemia. Specific anti-anthrax serum, which is presently the only known neutralizer of nonbound anthrax toxin, should be employed, in conjunction with bactericidal antibiotics, in treating cases of septicemic anthrax. However, anthrax antiserum is no longer commercially available in the United States. Penicillin can be given as a prophylactic in cases of known anthrax exposure. To prevent latent infection, penicillin prophylaxis should be coupled with vaccination.

Although anthrax is an ancient disease about which we have learned a great deal since the days of Robert Koch and Louis Pasteur, B. anthracis is still presenting us with challenging medical problems. Current research on B. anthracis genetics is providing answers to questions concerning toxin production and the molecular mechanisms of toxin activity in the host. Studies dealing with the evaluation of the protective efficacy of monoclonal antibodies, the application of recombinant DNA technology to the cloning of toxin components, and the development of biodegradable microcapsules for sustained release of vaccines, promise to advance our ability to prevent and to treat anthrax infections in man.

"...and it shall become fine dust over the land of Egypt and become boils breaking out in sores in man and beast throughout the land of Egypt."

(Exodus 9:9)

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